REMARKS

Claims 21 to 35 and 38 to 45 are pending in the application. Applicants have amended claims 34, 35, 40, and 41 to even more clearly recite the claimed invention. Applicants have amended claim 45 to track the language from amended claim 34, and to depend from amended claim 34. Claims 36, 37, and 46 have been canceled without prejudice or disclaimer. Claims 21 to 33 have been withdrawn from further consideration as being drawn to a non-elected invention. Claims 34 to 35 and 38 to 45 are currently under consideration.

Support for the amendments to claims 34 and 35 can be found in the specification, e.g., at page 6, lines 3 to 20; and at page 31, lines 17 to 25. Support for the amendment to claim 40 can be found in the specification, e.g., at page 4, lines 3 to 14. Support for the amendment to claim 41 can be found in the specification, e.g., at page 17, lines 2 to 27. Support for the amendment to claim 45 can be found in the specification, e.g., at page 6, lines 3 to 20. Those amendments add no new matter.

Objections to the Specification

The Examiner objected to the specification, alleging that "this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 because there is no sequence identifier for the nucleotide sequence in Figures 3-5 or in the 'BRIEF DESCRIPTION OF THE DRAWINGS'. Each nucleotide sequence is required to have a sequence identifier. Appropriate correction is required." Office Action ("Action"), at page 3.

Applicants note that Replacement Figures 3a, 3b, 4, and 5, which were filed with the application on March 9, 2004, include nucleotide sequence identifiers. Applicants

have amended the specification to insert sequence identification numbers. Applicants therefore respectfully request reconsideration and withdrawal of the objection.

Rejections under 35 U.S.C. § 112, second paragraph

First, the Examiner rejected claims 34 to 46 under 35 U.S.C. § 112, second paragraph. Action at page 3, item 4. Specifically, the Examiner alleged that the claims are "incomplete for omitting essential steps, such omission amounting to a gap between the steps." *Id.* The Examiner alleged that "[t]he omitted steps are: How to make a transgenic mouse comprising the vector from the selected ES cell comprising the vector, how to make a somatic transgenic mouse, how to make a germ line transgenic mouse, and how to administer the selected ES cell comprising the vector to make either a somatic transgenic mouse or a germ line transgenic [mouse]." *Id.*

Applicants respectfully traverse. The second paragraph of 35 U.S.C. § 112 states that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, second paragraph (West 2006). Definiteness of claim language under 35 U.S.C. § 112, second paragraph, must be analyzed in light of "[t]he claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." MPEP § 2173.02. The claims need not recite information presumed to be within the level of ordinary skill in the art where one of ordinary skill in the art to whom the specification and claims are directed would consider them clear. MPEP § 2164.08.

Without acquiescing in the rejection, and solely to expedite prosecution, Applicants have amended claim 34 to recite:

34. A method of making a transgenic mouse comprising a vector, comprising:

a) introducing a vector into a collection of mouse embryonic stem (ES) cells, wherein the vector comprises a 3´ gene trap cassette, comprising in operable combination:

i) a promoter;

ii) an exon sequence located 3´ from and expressed by said promoter, said exon sequence not encoding an activity conferring antibiotic resistance; and

iii) a splice donor sequence located at the 3´ end of said exon sequence;

wherein the vector does not encode a sequence that mediates the polyadenylation of an mRNA transcript encoded by said exon sequence;

b) selecting mouse ES cells that comprise the vector integrated into the genome;

c) identifying at least one mouse ES cell comprising the vector, wherein the integration of said vector results in the mutation of a gene of the mouse, and wherein the mutated gene has been identified after integration of the vector; and

d) making a transgenic mouse comprising the vector from at least one identified mouse ES cell that comprises the vector.

Each of claims 35 to 46 ultimately depends from claim 34.

Considering "[t]he claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made," one would not conclude that the claims are "incomplete for omitting essential steps, such omission amounting to a gap between steps." Applicants assert that one skilled in the art would understand the meaning of the claimed step of "making a transgenic mouse comprising the vector from at least one identified mouse ES cell that comprises the vector." Specifically, generation of transgenic animals from pluripotent ES cells transformed with recombinant vectors has been known since at least 1986. *See, e.g.,* Gossler et al., "Transgenesis by means of blastocyst-derived embryonic stem cell lines," PROC. NATL. ACAD. SCI. USA 83:9065-9069 (1986) (reporting the making of a transgenic mouse

resistant to neomycin using an ES expressing recombinant neomycin phosphotransferase) (enclosed).

Applicants assert that one skilled in the art would understand that "making a transgenic mouse comprising the vector from at least one identified mouse ES cell that comprises the vector" requires the introduction of at least one identified mouse ES cell that comprises the vector into a blastocyst by an appropriate method, such as injection, and then allowing the chimeric blastocyst to complete normal development. Specification at page 31, lines 17 to 25; Gossler et al., at 9065-66. That skilled artisan would also know that somatic and germ line transgenic mice are produced by the same method, and that somatic and germ line transgenic mice can be distinguished simply by mating the first generation transgenic animals to identify those that transmit the recombinant transgene to their progeny. Specification at page 56, line 27, to page 57, line 12; Gossler et al., at 9066-68.

Therefore, Applicants respectfully assert that the claims need not recite "How to make a transgenic mouse comprising the vector from the selected ES cell comprising the vector, how to make a somatic transgenic mouse, how to make a germ line transgenic mouse, and how to administer the selected ES cell comprising the vector to make either a somatic transgenic mouse or a germ line transgenic [mouse]." Action at page 3, item 4.

For at least the reasons discussed above, Applicants assert that claims 34 to 46 comply with the requirements of 35 U.S.C. § 112, second paragraph, and are not "incomplete for omitting essential steps, such omission amounting to a gap between the

steps." Action at page 3, item 4. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

Second, the Examiner alleged that the language "said splice acceptor" in claim 40 lacked antecedent basis. Action at page 3, item 5. Without acquiescing to the rejection, and solely to expedite prosecution, Applicants have amended claim 40 to recite "positioned between said promoter and an initiation codon of said exon sequence." That amendment should obviate the rejection of claim 40.

Applicants respectfully request reconsideration and withdrawal of the rejection of claim 40 under 35 U.S.C. § 112, second paragraph.

Third, the Examiner alleged that the language "said polyadenylation sequence" in claim 41 lacked antecedent basis. Action at page 3, item 6. Without acquiescing to the rejection, and solely to expedite prosecution, Applicants have amended claim 41 to recite "upstream of said promoter." That amendment should obviate the rejection of claim 41.

Applicants respectfully request reconsideration and withdrawal of the rejection of claim 41 under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 34 to 46 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Action at page 4, item 8. In particular, the Examiner alleged that "[t]he claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention." Action at page 4.

Applicants respectfully traverse. The test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." MPEP § 2164.01. Not everything necessary to practice the invention need be disclosed. MPEP § 2164.08. In fact, "what is well-known is best omitted." *Id.* Applicants will address each of the Examiner's contentions in turn below.

First, the Examiner alleged that "[t]he specification only discloses the preparation of [a] PGKbtkSD cassette and introduction of said cassette into embryonic stem cells (p. 61, 62)." Action at page 4.

Applicants respectfully traverse. The specification discloses more than "the preparation of a PGKbtkSD cassette and introduction of said cassette into embryonic stem cells." *Id.* For example, the specification discloses many different types of selectable markers, as well as various candidate promoters suitable for use in a 3' gene trap cassette including, but not limited to, cell- or tissue-specific promoters, viral promoters, and regulatable promoters. Specification at page 10, line 16, to page 12, line 4; and page 21, line 18, to page 22, line 6. The specification also discloses numerous criteria for selecting candidate natural exons, for designing synthetic exons, and for selecting and placing splice donor sequences for incorporation into a 3' gene trap cassette. Specification at page 22, line 7, to page 26, line 26. In addition, the specification discloses the use of different types of vectors, including vectors of viral and retroviral origin, as well as different methods of introducing a vector comprising a 3'

gene trap cassette into ES and other target cells including, but not limited to, commonly used methods of transfection. Specification at page 31, lines 5 to 16; and page 38, line 15, to page 40, line 35.

Second, the Examiner alleged that "[t]he specification fails to provide adequate guidance and evidence for how to make [and use] a somatic transgenic mouse or a germ line transgenic mouse comprising the claimed 3´ gene trap cassette by using murine ES cells." Action at page 5.

Specifically, the Examiner asserted that "[the] 3' gene trap vector is designed to integrate into introns or genes such that the gene integrated is over-expressed, silenced, or under-expressed, and a fusion protein encoded by the exon sequence in the vector and the exon sequence of the integrated gene is expressed." *Id.* The Examiner further argued that

> whether the integrated gene is over-expressed, suppressed, or under-expressed depends on the integration site of the 3' gene trap vector and its surrounding genomic sequence context. Whether a somatic transgenic mouse or a germ line transgenic mouse can be made or have a phenotype depends on how the integrated gene is expressed and what kind of gene product is expressed."

Id. The Examiner also contended that a silencer sequence at the integration site may result in no gene product, which would result in a mouse with a phenotype indistinct from a wild type mouse. *Id.*

The Examiner then focused on phenotypes of the produced mouse, alleging that "[a]bsent a phenotype of the transgenic mouse, one skilled in the art would not know how to use the transgenic mouse produced by the claimed method . . . ." *Id.* at page 6. The Examiner cited three articles as allegedly supporting a contention that a mouse

produced by the claimed method may have no phenotype and that any resulting phenotype would be unpredictable.[1] *Id.* at pages 6 to 8. The Examiner also contended that the claims encompass chimeric mice, and that such mice may have no phenotype other than wild type, and that any other phenotype would be unpredictable. *Id.* at pages 9 to 10.

Applicants respectfully traverse. The specification enables one skilled in the art to make a useful transgenic mouse by the claimed method without undue experimentation. One exemplary well-established utility for mice produced by the claimed method is to determine the effect of a particular genetic mutation on the efficacy of a drug. Applicants assert that one of ordinary skill in the art would have immediately appreciated that the claimed mice would be useful for at least that purpose at the time of filing. Applicants enclose copies of several publications that describe studies examining genotypic effects on drug efficacy. *See, e.g.,* Hawkins et al. (1996) "Inactivation of p53 enhances sensitivity to multiple chemotherapeutic agents." *Cancer Res.* 56:892-898; Link et al. (1996) "Cardiovascular regulation in mice lacking alpha2-adrenergic receptor subtypes b and c." *Science* 273:803-805. A more recent, high-profile example of such an effect is the disparate response of Brca1 positive and negative breast cancers to various treatments. *See, e.g.,* Jones et al. (2005) "Promotion of mammary cancer development by tamoxifen in a mouse model of Brca-1-

[1] Mogil *et al.,* "Heritability of nociception I: Responses of 11 inbred mouse strains on 12 measures of nociception," *Pain* 80:67-82 (1999); Sigmund, "Viewpoint: Are Studies in Genetically Altered Mice Out of Control?" *Arterioscl. Thromb. and Vasc. Biol.* 20:1425-29 (2000); and Leonard *et al.*, "Role of the Common Cytokine Receptor γ Chain in Cytokine Signaling and Lymphoid Development," *Immunol. Rev.* 148:97-114 (1995).

mutation-related breast cancer." *Oncogene* 24(22):3554-62 ("Jones"), a copy of which is enclosed.

First, usefulness of the transgenic mice to determine the effect of a particular genetic mutation on the efficacy of a drug does not depend on whether the integrated gene is "over-expressed, suppressed, or under-expressed." Any of those effects on an integrated gene could impact the efficacy of a drug. Thus, one may use the transgenic mice to determine the effect of a particular genetic mutation on the efficacy of a drug when the integrated gene is over-expressed, suppressed, or under-expressed.

Second, the Examiner improperly focuses on the alleged unpredictability of the phenotype produced. The present claims do not recite a particular phenotype. In fact, the claims make no mention of the phenotype of the claimed mice at all. Rather, the claims recite a method of making a transgenic mouse comprising the vector from at least one identified mouse ES cell, "wherein the integration of said vector results in the mutation of a gene of the mouse, and wherein the mutated gene has been identified after integration of the vector." Applicants assert that the specification teaches how to make a mouse having a vector integrated into its genome, e.g., at section 5.3.1, pages 31 to 32. Applicants further assert that the specification teaches how to identify the mutated gene, e.g., at section 5.3.2, pages 32 to 35. Since the claims do not recite a phenotype, there is no need for one skilled in the art to predict a phenotype, or even to characterize the phenotype once a transgenic mouse has been made by the claimed method.

Applicants assert that one skilled in the art could use transgenic mice produced by the claimed method without characterizing the phenotype at all. For example, as

discussed above, one skilled in the art could use a transgenic mouse made by the claimed method to determine the effect of the genotype of the mouse on the efficacy of a particular drug. Such methods were known in the art at the time of filing, as discussed above. The information gleaned from such methods is valuable for predicting the outcome of a particular therapy based on a patient's genetic profile. Moreover, that information is useful even where the genotype of the mouse has no effect on the efficacy of a drug, because it informs medical personnel that they need not be concerned with a patient's genotype at that locus when choosing that drug regimen.

Thus, enablement of the present claims does not require one skilled in the art to know or be able to predict the phenotype of transgenic mice made by the claimed method, or even to characterize the phenotype of the transgenic mice once they have been made. Rather, one skilled in the art need only be able to make and use a mouse comprising the vector from at least one identified mouse ES cell, "wherein the integration of said vector results in the mutation of a gene of the mouse, and wherein the mutated gene has been identified after integration of the vector." Applicants have demonstrated that the claimed method of making mice is enabled by the specification and/or the knowledge of one skilled in the art at the time of filing. Accordingly, applicants assert that the level of predictability in the art with respect to a phenotype is not relevant to the analysis of enablement of the present claims.

Finally, the Examiner alleged that Houdebine, L.-M., "The methods to generate transgenic animals and to control transgene expression," *J. Biotechnol.* 98:145-60 (2002) ("Houdebine"), supports the propositions that "'animal transgenics [are] still suffering from technical limitations' (e.g., abstract). Gene replacement by homologous

recombination in somatic mammalian cells has relatively poor efficiency'" and "'For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells' (e.g. p. 148, right column)." Action at page 8.

The Examiner further alleged that "gene transfer or inactivation using embryonic cells has failed in species other than mouse." Action at page 8. The Examiner also appears to allege that Houdebine suggested that there were similar failures in mouse lines other than two particular lines. *Id.* The Examiner concluded that "the claimed method of using murine embryonic stem cells to make mutant mice via 3´ gene trap cassette at the time of the invention was not enabled other than the use of the two mouse lines mentioned by Houdebine." Action at pages 8-9.

First, the Examiner alleged that "[m]urine embryonic stem cells include mouse and rat embryonic stem cells." Action at page 8. Solely to expedite prosecution and without acquiescing to the rejection, Applicants have amended claims 34 and 35 to recite "mouse ES cells." Thus, any teaching of Houdebine concerning rats is not applicable to the present claims.

Second, Houdebine discusses difficulties involving species other than mouse and notes that transmission of mutations to progeny has been observed so far in only two mouse lines. The Examiner, however, fails to explain why one skilled in the art would consider that the presently claimed methods could only be practiced on those two mouse lines without undue experimentation. While pointing out an observation of success in only two mouse lines, Houdebine does not indicate that one skilled in the art would expect failure in other mouse lines without undue experimentation.

For at least these reasons, Applicants assert that claims 34 to 46 comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Therefore Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. § 102(e)

The Examiner rejected claims 34 to 39 and 42 to 46 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,207,371, to Zambrowicz *et al.* ("the '371 patent"). Action at page 10. The Examiner alleged that the '371 patent "has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. § 102(e)." *Id.*

Without acquiescing to the rejection, and solely to expedite prosecution of this application, Applicants enclose a declaration under 37 C.F.R. § 1.132 signed by Brian Zambrowicz ("Zambrowicz"), Glenn A. Friedrich ("Friedrich"), and Arthur T. Sands ("Sands"). The declaration states that Zambrowicz, Friedrich, and Sands are three of four inventors named on the '371 patent. The declaration also states that Zambrowicz, Friedrich, and Sands are three of four inventors on the present U.S. patent application. The declaration further states that Zambrowicz, Friedrich, and Sands understand that the Examiner has rejected claims 34 to 39 and 42 to 46 of the present U.S. patent application in view of certain material disclosed in the '371 patent. Specifically, the declaration states that Zambrowicz, Friedrich, and Sands understand that the Examiner stated that

> [The '371 patent] discloses VICTR3-5 gene trap vectors comprising a promoter, such as PGK promoter, a selectable marker, such as βgeo or HSV-Tk, and a splice donor sequence (e.g. column 7, lines 20-21,

> paragraph bridging columns 9-10, column 15, lines 41-54). The gene trap vector can be represented in retroviral form in retroviral vectors (e.g. column 7-8). Mouse ES cells are transfected with the gene trap vector to introduce mutation in the gene of the mouse genome and the ES cells can be injected into a blastocyst and become incorporated into normal development and ultimately the germ line so as to produce mutant transgenic m[ic]e (e.g. column[s] 15-16). [The '371 patent] further teaches identifying mutated gene sequence in the genome by RT-PCR [with] the mRNA isolated from the ES cells and using primers specific to the trapped, fusion transcript for PCR amplification and sequencing reaction to determine the sequence of the fusion transcript (e.g. section 5.2.2, column[s] 16-17).

Action at pages 11 to 12.

The declaration states that Zambrowicz, Friedrich, and Sands are the sole inventors of claims 34 to 39 and 42 to 46, with the amendments set forth above. The declaration also states that Zambrowicz, Friedrich, and Sands are the sole inventors of the material in the '371 patent cited by the Examiner and quoted above. The declaration further states that Allen Bradley, the fourth inventor named on the '371 patent, is not an inventor of the material in the '371 patent cited by the Examiner and quoted above. The declaration also states that Stan Lilleberg, the fourth inventor named on the present U.S. patent application, is not an inventor of currently rejected claims 34 to 39 and 42 to 46 in the present U.S. patent application. Thus, the material from the '371 patent cited by the Examiner at pages 11 to 12 of the Action, it is not the work of another. Thus, the '371 patent cannot be prior art under § 102(e).

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 34 to 39 and 42 to 46 under 35 U.S.C. § 102(e).

Conclusion

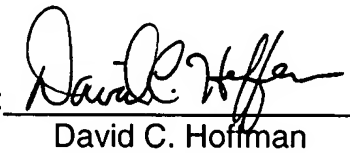
Applicants respectfully assert that the application is in condition for allowance and request issuance of a Notice of Allowance. If the Examiner does not consider the application to be in condition for allowance, applicants request that she call the undersigned at (650) 849-6617 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 18, 2007

By: 

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